PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
Le A 33 298-WO BU		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/06991	21/09/1999	25/09/1998
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant BAYER AKTIENGESELLSCHAFT et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14/04/2000	27.12.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Rojo Romeo, E Telephone No. +49 89 2399 7321

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/06991

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-45 as originally filed

Claims, No.:

1-12 as originally filed

Drawings, sheets:

1/42-42/42 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☒ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

   Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 10, 11 (entirely); 9, 12 (partially).

because:

   ☒ the said international application, or the said claims Nos. 9, 12 (partially) relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion

could be formed.

☒ no international search report has been established for the said claims Nos. 10, 11.

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:
see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-8 (entirely); 9, 12 (partially).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-8, 9, 12
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-8, 9, 12

Industrial applicability (IA) Yes: Claims 1-8, 9, 12
No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item II

Priority

The priority document fails to provide the sequence encoding the human ABCA1 protein (SEQ ID NO: I and 2).
Consequently, priority cannot be acknowledged.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 10 and 11 were not searched by the International Search Authority, and thus, are not examined.

Moreover, since the Applicant failed to pay additional fees, only invention 1 is examined. Claims 9 and 12 are only examined as far as they concern subject-matter directed to said first invention.

Re Item IV

Lack of unity of invention

The International Examination Authority agrees with the objection for lack of unity raised by the International Searching Authority. The present application concerns 3 different inventions:

invention 1 (claims 1-8 complete; 9, 12 partially):
A polynucleotide comprising a member selected from the group consisting of a polynucleotide encoding SEQ ID NO: 2, a polynucleotide capable of hybridizing with this one and at least 70% identical to it, and a polynucleotide fragment of any of the two previous ones, the said polynucleotide wherein the polynucleotide is DNA; a vector comprising one or more of the mentioned polynucleotide, a host cell containing the vector and a process for producing a polypeptide encoded by said DNA; a polypeptide selected from a group consisting of a polypeptide having the deduced amino acid sequence of SEQ ID NO: 2 and fragments, analogs and derivatives thereof, a polypeptide comprising amino acid 1 to amino acid 2201 of SEQ ID NO: 2; an antibody capable to bind said polypeptide; a diagnostic kit for the detection of said polypeptide. The use of a polypeptide encoded by a polynucleotide comprising a member selected from the group consisting of a polynucleotide as set forth in SEQ ID NO: 1, a polynucleotide capable of hybridizing with

this one and at least 70% identical to it, and a polynucleotide fragment of any of those two in an assay for detecting modulators of said polypeptide; modulator of a polypeptide encoded by a polynucleotide as set forth in SEQ ID NO: 1, a polynucleotide capable of hybridizing with this one and at least 70% identical to it, and a polynucleotide fragment of any of those two; a pharmaceutical comprising the modulator. An assay for detecting polypeptides encoded by a polynucleotide comprising a member selected from the group consisting of a polynucleotide as set forth in SEQ ID NO: 1, a polynucleotide capable of hybridizing with this one and at least 70% identical to it, and a polynucleotide fragment of any of those two.

invention 2 (claim 9, partially)
Use of a polypeptide encoded by a polynucleotide comprising a member selected from the group consisting of a polynucleotide as set forth in SEQ ID NO: 3, 4, 6 to 31, a polynucleotide capable of hybridizing to this one and a fragment of any of those two in an assay for detecting modulators of said polypeptides.

invention 3 (claim 12, partially)
An assay for detecting polypeptides encoded by a polynucleotide comprising a member selected from the group consisting of a polynucleotide as set forth in SEQ ID NO: 3, 4, 6 to 32 and 54, polynucleotide capable of hybridizing to this one and which is at least 70% identical to it, and a fragment of any of those two.

In the view of the fact that the methods for isolating polynucleotide sequences coding for human ABC transporters, the production of the latter by recombinant DNA technology and the uses thereof in diagnosis and in screening to find modulators of the said polypeptides are already disclosed in the prior art, due to the essentially different nature of the three problems and their corresponding solutions, and due to the fact that no other technical features can be distinguished which in the light of the prior art, could be regarded as special technical features, the IPEA is of the opinion that there is no single inventive concept underlying the plurality of claimed inventions of the present application in the sense of Rule 13.1 PCT. In addition, invention 2 and invention 3 may be split into 28 and 30 different inventions, respectively, corresponding to the different sequences claimed, said sequences having as mere relation the fact that they encode ABC transporters, fragments thereof or untranslated regions of such genes.
As mentioned in Re Item III, only invention 1 is examined.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents, cited in the International Search Report:

D1: LUCIANI ET AL.: 'Cloning of Two Novel ABC Transporters Mapping on Human Chromosome 9.' GENOMICS, vol. 21, 1 May 1994 (1994-05-01), pages 150-159, XP000869719

D2: WO 98 37764 A (BAYLOR COLLEGE MEDICINE ;UNIV UTAH (US); US GOVERNMENT (US); UNIV) 3 September 1998 (1998-09-03)

D3: LANGMANN, THOMAS ET AL: 'Molecular cloning of the human ATP-binding cassette transporter 1 (hABC1) evidence for sterol-dependent regulation in macrophages' BIOCHEM. BIOPHYS. RES. COMMUN. (1999), 257(1), 29-33,2 April 1999 (1999-04-02), pages 29-33, XP002127984

Documents cited by the Examiner:

D4: Rust et al.: "Assignment of Tangier disease to chromosome 9q31 by a graphical linkage exclusion strategy. Nature Genet. 20, 9698, September 1998.

D5: Brooks-Wilson et al.: "Mutations in ABC1 in Tangier disease and familial high-density lipoprotein deficiency. Nature Genet. 22, 336-345, August 1999.

A copy of the last two documents is annexed to this Report.

The present application discloses the 6603 base pair long nucleotide sequence of the cDNA for the human ATP-binding cassette transporter ABC1 encoding a 2201 amino acid long protein (hABC1; SEQ ID No.: 1 and 2; example 6 and Fig. 8). The protein displays a 94% identity on the amino acid level in an alignment with mouse ABCA1.

The examples given concern the tissue distribution of hABC1, the sterol regulation of hABC1 mRNA expression (induction by cholesterol loading and down-regulation by cholesterol depletion), cloning of the hABC1 cDNA from mononuclear phagocytes, the expression of hABC1 during keratinocytic cell (HaCAT) differentiation (low expression) in example 9, and relation between mutations in the hABC1 gene and Tangier disease (example 10).

1. Novelty (Art. 33(2) PCT)

1.1 Documents D1 and D3 describe the cloning of the human ABC1 transporter and disclose the sequences corresponding to SEQ ID No.: 1 and 2 . Moreover, in D3, the protein hABC1 and antibodies directed against it are described (e.g. Fig 2 in D3). Consequently, claims 1-4 and 6-8 lack novelty over these two documents.

1.2 The subject-matter of claim 5 can be considered as a trivial embodiment of the preceding claims and, therefore, also lacks novelty over D1 and D3.

1.3 Concerning claim 8, the wording "diagnostic kit" does not provide any technical feature necessary to distinguish the subject-matter of this claim from that of claim 7 (an antibody capable of detecting the polypeptide of claim 6, see VIII). Thus, the subject-matter was read as being that of claim 7, which is not novel.

1.4 Moreover, the Applicant's attention is drawn to the fact that "a polynucleotide fragment of the polynucleotide of (a) or (b)" as claimed in claim 1 can be as small as two nucleotides and thus any existing polynucleotide may possess 2 consecutive nucleotides as found in SEQ ID No. 1 (see VIII). Also for this reason, claim 1 lacks novelty.

Similarly, concerning claim 6, any amino acid may constitute a fragment of the polypeptide of SEQ ID No.: 2 and thus, constitute novelty destroying prior art for this claim.

This reasoning also applies to claims 9 and 12. Consequently, these claims also lack novelty.

In summary, claims 1-9 and 12 lack novelty over documents D1 and D3 and, thus, are neither inventive.

2 Inventive step (art. 33(3) PCT)

D3 discloses a polynucleotide and polypeptide for hABC1. Moreover, it was known from D4 and D5, that hABC1 was linked with the Tangier disease and that mutations in this gene were responsible for this disease. Thus, the need for agents interacting with this transporter as potential therapeutic agents was known from prior art. In D2, methods for the detection of agents which alter a (retina-specific) ATP binding cassette transporter are disclosed. The person skilled in the art would combine the

teaching of this document with that of D3 to screen for agents capable of interacting and modulating the activity of hABC1. Thus, the IPEA fails to see any inventive activity in the subject-matter of current claims 1-9 and 12.

Re Item VI

Certain documents cited

Since the right of priority is not valid for the examined first group of inventions, D4 and D5 belong to the state of the art according to Art. 33(2) PCT.

Re Item VIII

Certain observations on the international application

1. Clarity (Art. 6 PCT)

1.1 Concerning claim 1, a polynucleotide fragment can be as small as 2 nucleotides and thus, any polynucleotide is likely to contain 2 consecutive nucleotides as in SEQ ID No.: 1. This objection applies to claims 9(c) and 12(c).

1.2 Concerning claim 6, the terms " fragments, analogs and derivatives thereof" are vague and subject to interpretation. Indeed, fragments of an amino acid region can be as small as 1 amino acid and thus, be present in any known protein.
In addition, the term "analog" is unclear since analogy could occur at the structural level (degree of identity/homology) or at the functional level. Without specification, the scope of the claim is unclear.
Moreover, concerning the term "derivative", the Applicant's attention is drawn to the fact that any protein or nucleic acid can be seen as the "derivative" of any other by a certain number and type of modifications (deletions, additions, substitutions, etc). Therefore, claim 6 is ambiguous.

1.3 In view of the high percentage of homology existing between the different ATP binding cassette transporters, in particular in the transmembrane regions, any known antibody directed to an ATP binding cassette transporter may be binding to the hABC1 transporter. Therefore, in the absence of evidence that the claimed antibody shows specificity for the claimed hABC1, the scope of claim 7 also encompasses these antibodies.

1.4 Claims 8, 9 and 12 do not meet the requirements of Article 6 PCT in that the matter

for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result are missing.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
Le A 33 298		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 99/06991	21/09/1999	25/09/1998
Applicant		
BAYER AKTIENGESELLSCHAFT et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 8 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [X] contained in the international application in written form.

   [X] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. -

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/06991

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 10,11
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

INVITATION TO PAY ADDITIONAL FEES

National application No.
PCT/EP 99/06991

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: (1-8) - complete, (9, 12) - partially

A polynucleotide comprising a member selected from the group consisting of a polynucleotide encoding SEQ ID NO:2, a polynucleotide capable of hybridizing with this one and at least 70% identical to it, and a polynucleotide fragment of any of the two previous ones; the said polynucleotide wherein the polynucleotide is DNA; a vector comprising one or more of the any of the mentioned polynucleotides, a host cell containing the vector and a process for producing a polypeptide comprising expressing from that host cell the polypeptide encoded by said DNA; a polypeptide selected from a group consisting of a polypeptide having the deduced amino acid sequence of SEQ ID NO:2 and fragments, analogs and derivatives thereof, and a polypeptide comprising amino acid 1 to amino acid 2201 of SEQ ID NO:2; an antibody capable to bind said polypeptide; a diagnostic kit for the detection of said polypeptide. The use of a polypeptide encoded by a polynucleotide comprising a member selected from the group consisting of a polynucleotide as set forth in SEQ ID NO: 1, a polynucleotide capable of hybridizing to this one and which is at least 70% identical to it, and a fragment of any of those two in an assay for detecting modulators of said polypeptide; modulator of a polypeptide encoded by a polynucleotide selected from the group consisting of a polynucleotide as set forth in SEQ ID NO:1, a polynucleotide capable of hybridizing to this one and which is at least 70% identical to it, and a fragment of any of those two; a pharmaceutical comprising the modulator. And an assay for detecting polypeptides encoded by a polynucleotide comprising a member selected from the group consisting of a polynucleotide as set forth in SEQ ID NO:1, a polynucleotide capable of hybridizing to this one and which is at least 70% identical to it, and a fragment of any of those two.

2. Claims: 9 - partially

Use of a polypeptide encoded by a polynucleotide comprising a member selected from the group consisting of a polynucleotide as set forth in SEQ ID NO: 3, 4 and 6 to 31, a polynucleotide capable of hybridizing to this one and which is at least 70% identical to it, and a fragment of any of those two in an assay for detecting modulators of said polypeptide; modulator of a polypeptide encoded by a polynucleotide selected from the group consisting of a polynucleotide as set forth in SEQ ID NO: 3, 4 and 6 to 31, a polynucleotide capable of hybridizing to this one and which is at least 70% identical to it, and a fragment of any of those two; a pharmaceutical comprising the modulator.

3. Claims: 12 - partially

An assay for detecting polypeptides encoded by a polynucleotide comprising a member selected from the group consisting of a polynucleotide as set forth in SEQ ID NO: 3, 4, 6 to 32 and 54, a polynucleotide capable of hybridizing to this one and which is at least 70% identical to it, and a fragment of any of those two.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 10,11

Claims 10 and 11 refer to an agonist/antagonist of the polypeptides without giving a true technical characterization. In consequence, the scope of said claims is vague and ambiguous and their subject matter is not sufficiently disclosed and supported (Art. 5 and 6 PCT). No search can be carried out for purely speculative claims whose wording is, in fact, a mere recitation of the results to be achieved.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/06991

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/12 C07K14/705 C07K16/28 A61K38/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LUCIANI ET AL.: "Cloning of Two Novel ABC Transporters Mapping on Human Chromosome 9." GENOMICS, vol. 21, 1 May 1994 (1994-05-01), pages 150-159, XP000869719 page 152, column 1, paragraph 5 -page 153, column 1, paragraph 3 figure 4, top (ABC1) ---	1-7,12
X	WO 98 37764 A (BAYLOR COLLEGE MEDICINE ;UNIV UTAH (US); US GOVERNMENT (US); UNIV) 3 September 1998 (1998-09-03) abstract claims 29,40 --- -/--	8,9,12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 April 2000	19.05.00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mata Vicente, T.

4

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 48797 A (GENZYME CORP) 24 December 1997 (1997-12-24) page 65, paragraph 3 claims 30-56	9,12
X	HOLZINGER A ET AL: "cDNA cloning and mRNA expression of the human adrenoleukodystrophy related protein (ALDRP), a peroxisomal ABC transporter" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS,US,ACADEMIC PRESS INC. ORLANDO, FL, vol. 239, pages 261-264, XP002091087 ISSN: 0006-291X page 261, column 2, paragraph 2 -page 262, column 1, paragraph 1 page 264, column 1, paragraph 2	9,12
X	ALLIKMETS R ET AL: "CHARACTERIZATION OF THE HUMAN ABC SUPERFAMILY: ISOLATION AND MAPPING OF 21 NEW GENES USING THE EXPRESSED SEQUENCE TAGS DATABASE" HUMAN MOLECULAR GENETICS,GB,OXFORD UNIVERSITY PRESS, SURREY, vol. 5, no. 10, pages 1649-1655, XP002074412 ISSN: 0964-6906 page 1654, column 1, paragraph 4 -column 2, paragraph 1	12
X	MICHIELI M ET AL: "RESTORING UPTAKE AND RETENTION OD DAUNORUBICIN AND IDARUBICIN IN P170-RELATED MULTIDRUG RESISTANCE CELLS BY LOW CONCENTRATION D-VERAPAMIL, CYCLOSPORIN-A AND SDZ PSC 833" HAEMATOLOGICA,IT,ROME, vol. 79, no. 6, page 500-507 XP000617792 page 500, column 2, paragraph 2 -page 501, column 1, paragraph 2	9
X	RAO V V ET AL: "A Novel Areneisonitrile Tc Complex Inhibits the Transport Activity of MDR P-Glycoprotein - Direct binding of verapamil to P-glycoprotein on specific sites and transport of verapamil outward across the plasma membrane of K562/ADM cells" NUCLEAR MEDICINE AND BIOLOGY,US,ELSEVIER SCIENCE PUBLISHERS, NEW YORK, NY, vol. 25, no. 3, page 225-232 XP004113279 ISSN: 0969-8051 page 229, column 2, paragraph 3	9

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4

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WATANABE T ET AL: "COMPARATIVE STUDY ON REVERSAL EFFICACY OF SDZ PSC 833, CYCLOSPORIN A AND VERAPAMIL ON MULTIDRUG RESISTANCE IN VITRO AND IN VIVO" ACTA ONCOLOGICA,XX,XX, vol. 34, no. 2, page 235-241 XP000617807 abstract	9
X	KLUGBAUER ET AL.: "Primary structure of a novel ABC transporter with a chromosomal localization on the band encoding the multidrug resistance-associated protein." FEBS LETT, vol. 391, 1996, pages 61-65, XP002136624 page 61, column 2, paragraph 3	12
X	WO 94 22846 A (PFIZER ;ARNOLD LEE D (US); COE JOTHAM W (US); KANEKO TAKUSHI (US);) 13 October 1994 (1994-10-13) abstract	9
P,X	LANGMANN, THOMAS ET AL: "Molecular cloning of the human ATP-binding cassette transporter 1 (hABC1) evidence for sterol-dependent regulation in macrophages" BIOCHEM. BIOPHYS. RES. COMMUN. (1999), 257(1), 29-33,2 April 1999 (1999-04-02), pages 29-33, XP002127984 abstract figure 1	1-9,12
A	LU, J. F. ET AL.: "A mouse model for X-linked adrenoleukodystrophy." PNAS, vol. 94, August 1997 (1997-08), pages 9366-9371, XP002136625 abstract	9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/06991

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9837764 A	03-09-1998	AU 6538698 A	18-09-1998
		EP 0989805 A	05-04-2000
WO 9748797 A	24-12-1997	US 6028173 A	22-02-2000
		US 6030806 A	29-02-2000
		AU 1831497 A	07-01-1998
		EP 0914424 A	12-05-1999
WO 9422846 A	13-10-1994	FI 941452 A	01-10-1994

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For Receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* Le A 33 298-WO Bu

Box No. I TITLE OF INVENTION

ATP binding cassette genes and proteins for diagnosis and treatment of lipid disorders and inflammatory diseases"

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BAYER AKTIENGESELLSCHAFT
51368 Leverkusen
DE

☐ This person is also inventor.

Telephone No.
0214 30 71166

Facsimile No.
0214 30534 82

Teleprinter No.
85 101-265byd

State *(that is, country)* of nationality:
DE

State *(that is, country)* of residence:
DE

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Schmitz, Gerd
Turmstrasse 15a
D 93161 Sinzing
DE

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:
DE

State *(that is, country)* of residence:
DE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☐ agent ☒ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BAYER AKTIENGESELLSCHAFT
51368 Leverkusen, DE

Telephone No.
0214 30 71166

Facsimile No.
0214 30534 82

Teleprinter No.
85 101-265byd

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Klucken, Jochen
Silberne Fischgasse 13
D 93047 Regensburg
DE

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: DE

State *(that is, country)* of residence: DE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

---

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

---

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

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Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

---

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- ☒ AP **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP **European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☒ AE United Arab Emirates
- ☒ AL Albania .....
- ☒ AM Armenia .....
- ☒ AT Austria .....
- ☒ AU Australia .....
- ☒ AZ Azerbaijan
- ☒ BA Bosnia and Herzegovina .....
- ☒ BB Barbados
- ☒ BG Bulgaria .....
- ☒ BR Brazil .....
- ☒ BY Belarus .....
- ☒ CA Canada
- ☒ CH and LI Switzerland and Liechtenstein
- ☒ CN China .....
- ☒ CU Cuba .....
- ☒ CZ Czech Republic .....
- ☒ DE Germany .....
- ☒ DK Denmark .....
- ☒ EE Estonia .....
- ☒ ES Spain .....
- ☒ FI Finland .....
- ☒ GB United Kingdom
- ☒ GD Grenada
- ☒ GE Georgia .....
- ☒ GH Ghana .....
- ☒ GM Gambia
- ☒ HR Croatia .....
- ☒ HU Hungary .....
- ☒ ID Indonesia
- ☒ IL Israel .....
- ☒ IN India .....
- ☒ IS Iceland
- ☒ JP Japan .....
- ☒ KE Kenya .....
- ☒ KG Kyrgyzstan .....
- ☒ KP Democratic People's Republic of Korea .....
- ☒ KR Republic of Korea .....
- ☒ KZ Kazakhstan .....
- ☒ LC Saint Lucia
- ☒ LK Sri Lanka
- ☒ LR Liberia
- ☒ LS Lesotho .....
- ☒ LT Lithuania
- ☒ LU Luxembourg
- ☒ LV Latvia
- ☒ MD Republic of Moldova .....
- ☒ MG Madagascar .....
- ☒ MK The former Yugoslav Republic of Macedonia .....
- ☒ MN Mongolia
- ☒ MW Malawi .....
- ☒ MX Mexico .....
- ☒ NO Norway
- ☒ NZ New Zealand .....
- ☒ PL Poland .....
- ☒ PT Portugal .....
- ☒ RO Romania
- ☒ RU Russian Federation .....
- ☒ SD Sudan
- ☒ SE Sweden
- ☒ SG Singapore
- ☒ SI Slovenia .....
- ☒ SK Slovakia .....
- ☒ SL Sierra Leone .....
- ☒ TJ Tajikistan .....
- ☒ TM Turkmenistan .....
- ☒ TR Turkey .....
- ☒ TT Trinidad and Tobago .....
- ☒ UA Ukraine .....
- ☒ UG Uganda .....
- ☒ US United States of America .....
- ☒ UZ Uzbekistan .....
- ☒ VN Viet Nam .....
- ☒ YU Yugoslavia .....
- ☒ ZA South Africa .....
- ☒ ZW Zimbabwe .....

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

☒ and all the countries which have acceded to the PCT by and on the filing date of this application .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. If, in any of the Boxes, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

*(i) **if more than two persons are involved as applicants and/or inventors** and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;*

*(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication **"the States indicated in the Supplemental Box"** is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*

*(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, **the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America**: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*

*(iv) if, in addition to the agent(s) indicated in Box No. IV, there are **further agents**: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*

*(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication **"patent of addition,"** or **"certificate of addition,"** or if, in Box No. V, the name of the United States of America is accompanied by an indication **"continuation"** or **"continuation-in-part"**: in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*

*(vi) if, in Box No. VI, there are **more than three earlier applications whose priority is claimed**: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;*

*(vii) if, in Box No. VI, **the earlier application is an ARIPO application**: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed.*

*2. If, with regard to the **precautionary designation statement** contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.*

*3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning **non-prejudicial disclosures or exceptions to lack of novelty**: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.*

Continuation of Box No IX

Gerd Schmitz

Jochen Klucken

Box No. VI PRIORITY CL ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) (25.09.1998) 25. September 1998	60/101,706	US		
item (2)				
item (3)				

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): _____

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA /

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	:	5
description (excluding sequence listing part)	:	45
claims	:	2
abstract	:	1
drawings	:	42
sequence listing part of description	:	63
Total number of sheets	:	158

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☒ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other *(specify)*: Debit order, Demand for publication copies

Figure of the drawings which should accompany the abstract:

Language of filing of the international application:

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Bayer Aktiengesellschaft

for further signatures please see supplemental sheet will follow

Dr. Knud Schauerte Dr. Frank Burkert

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	☐ received:
4. Date of timely receipt of the required corrections under PCT Article 11(2):	☐ not received:
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau: